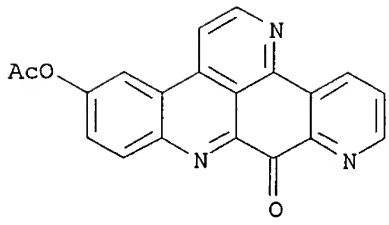


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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                      -2.60      -2.60

FILE 'REGISTRY' ENTERED AT 17:38:34 ON 28 APR 2003
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 APR 2003  HIGHEST RN 506405-59-0
DICTIONARY FILE UPDATES:  27 APR 2003  HIGHEST RN 506405-59-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s ascididemin
L4            8 ASCIDIDEMIN

=> d l4 1-8

L4   ANSWER 1 OF 8  REGISTRY  COPYRIGHT 2003 ACS
RN   155107-79-2  REGISTRY
CN   9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one, 5-nitro- (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   3-Nitroascididemin
FS   3D CONCORD
MF   C18 H8 N4 O3
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER
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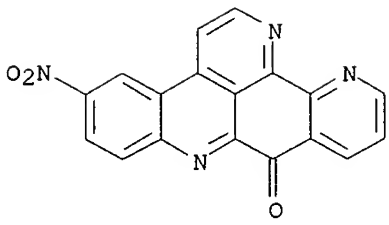

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2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 2 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 155107-78-1 REGISTRY
CN 9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one, 7-nitro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **1-Nitroascididemin**
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FS 3D CONCORD
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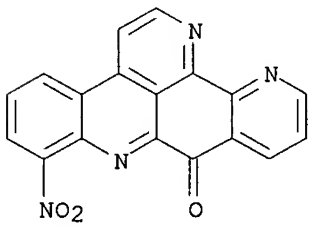
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 3 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 150222-09-6 REGISTRY
CN 9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one, 10-methoxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **11-Methoxyascididemin**
CN CRL 8368
FS 3D CONCORD
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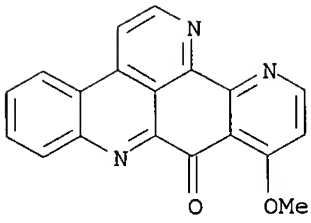
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 143370-23-4 REGISTRY
CN 9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one, 5-methoxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **3-Methoxyascididemin**
CN Neocalliactine methyl ether
CN O-Methylneocalliactine
FS 3D CONCORD
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LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, TOXCENTER
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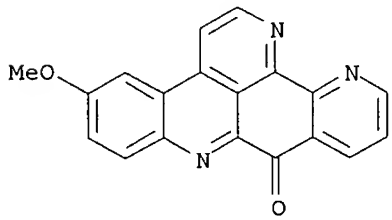
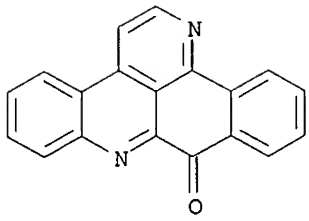


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

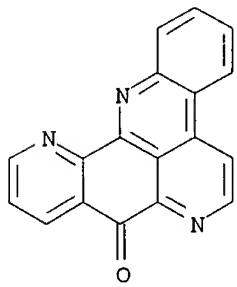
L4 ANSWER 5 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 143091-80-9 REGISTRY
CN 9H-Benzo[b]pyrido[4,3,2-mn]acridin-9-one (9CI) (CA INDEX NAME)
OTHER NAMES:
CN BC 1-31
CN Benzosampangine
CN Benzo[4,5]sampangine
CN **N-8-Deazaascididemin**
FS 3D CONCORD
MF C19 H10 N2 O
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12 REFERENCES IN FILE CA (1957 TO DATE)
12 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 6 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 133400-90-5 REGISTRY
CN 8H-Benzo[b]pyrido[4,3,2-de][1,10]phenanthrolin-8-one (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Isoascididemin**
FS 3D CONCORD
MF C18 H9 N3 O
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMINFORMRX
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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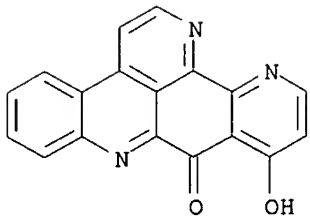
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

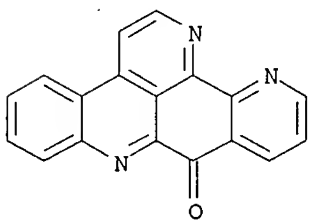
L4 ANSWER 7 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 129741-41-9 REGISTRY
CN 9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one, 10-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **11-Hydroxyascididemin**
CN 11-Hydroxyascididemine
CN CRL 8387
FS 3D CONCORD
MF C18 H9 N3 O2
CI COM
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1957 TO DATE)
9 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 8 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 114622-04-7 REGISTRY
CN 9H-Quino[4,3,2-de][1,10]phenanthrolin-9-one (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Ascididemin**
CN Ascididemine
CN CRL 8274
CN Leptoclinidinone
CN NSC 675670
FS 3D CONCORD
DR 109802-18-8
MF C18 H9 N3 O
SR CA
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMINFORMRX, EMBASE, NAPRALERT, TOXCENTER
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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33 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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FULL ESTIMATED COST	18.46	187.05
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CA SUBSCRIBER PRICE	0.00	-2.60

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FILE COVERS 1907 - 28 Apr 2003 VOL 138 ISS 18
FILE LAST UPDATED: 27 Apr 2003 (20030427/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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396303 ?TUMOR?
L6 17 L5 AND ?TUMOR?

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L7 0 L5 AND ?TUMOUR?

=> d l6 1-9 ibib abs

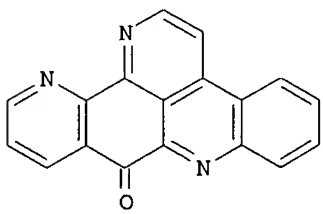
L6 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:62847 CAPLUS
DOCUMENT NUMBER: 138:248103
TITLE: Mechanism of Ascididemin-Induced Cytotoxicity
AUTHOR(S): Matsumoto, Sandra S.; Biggs, Jason; Copp, Brent R.; Holden, Joseph A.; Barrows, Louis R.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Chemical Research in Toxicology (2003), 16(2), 113-122
CODEN: CRTOEC; ISSN: 0893-228X
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Some marine animals are rich sources of unique polycyclic arom. alkaloids that are cytotoxic against **tumor** cell lines and effective in mouse **tumor** xenograft models. Ascididemin is a pyridoacridine alkaloid originally derived from a Didemnum sp. tunicate. It has potent cytotoxicity against **tumor** cells in vitro and in vivo. Preclin. screening at NCI revealed the antineoplastic activities of ascididemin and a synthetic analog. Ascididemin has been reported to inhibit topoisomerase II and induce topoisomerase II-mediated DNA cleavage. This study, however, focuses on the unique ability of ascididemin and two synthetic analogs to cleave DNA in the absence of topoisomerase I or II. An in vitro assay revealed their concn.-dependent ability to cleave DNA and identified dithiothreitol as the sole requirement for maximal activity. On the basis of shared structural features of the three

analogs, a double N-bay region and iminoquinone heterocyclic ring, two possible mechanisms of action were hypothesized: (1) generation of reactive oxygen species facilitated by metal binding to the common phenanthroline bay region, and (2) prodn. of reactive oxygen species by direct redn. of the iminoquinone moiety. Exptl. results supported direct iminoquinone redn. and ROS generation as the mechanism of ascididemin cytotoxicity. Antioxidants protected against DNA cleavage in vitro and protected cultured Chinese hamster ovary cells from toxicity. Addnl., it was shown that cells deficient in the ability to repair reactive oxygen species damage to their DNA were more susceptible to ascididemin and analogs than repair competent cells. Ascididemin-treated cells were also shown to induce oxygen-stress related proteins, further implicating the prodn. of reactive oxygen species as the mechanism of cytotoxicity for these mols.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:525769 CAPLUS
DOCUMENT NUMBER: 137:217121
TITLE: Synthesis and In Vitro **Antitumor** Activity of Novel Ring D Analogues of the Marine Pyridoacridine Ascididemin: Structure-Activity Relationship
AUTHOR(S): Delfourne, Evelyne; Darro, Francis; Portefaix, Philippe; Galaup, Chantal; Bayssade, Sylvie; Bouteille, Anne; Le Corre, Laurent; Bastide, Jean; Collignon, Francoise; Lesur, Brigitte; Frydman, Armand; Kiss, Robert
CORPORATE SOURCE: Centre de Phytopharmacie-, UMR-CNRS 5054, Universite de Perpignan, Perpignan, 66860, Fr.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3765-3771
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:217121
GI



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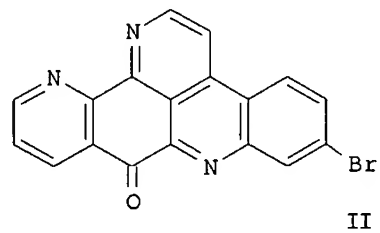

II

AB Marine compds. with pyridoacridine skeletons are known to exhibit interesting **antitumor** activities. Ascididemin has already been reported as displaying significant **antitumor** activities in vitro and has also been found to have a relatively high global toxicity in vivo. We synthesized a series of 16 analogs (among which 11 compds. were different from previously described ones) with the aim of developing new anticancer agents with significantly improved efficacy/tolerability ratios. These compds. were obtained either by total synthesis from

5,8-quinolinedione and substituted 2-aminoacetophenones or by the direct substitution of ascididemin (I). The different compds. and ascididemin used as the control compd. were tested at six different concns. on 12 different human cancer cell lines of various histopathol. types (glioblastomas and breast, colon, lung, prostate, and bladder cancers). The IC50 value (i.e., the drug concn. inhibiting the mean growth value of the 12 cell lines by 50%) of these compds. ranged over five log concns., i.e., between 10 000 and 0.1 nM. For several new chem. entities, the **antitumor** activity (detd. in vitro) and tolerability (detd. in vivo) were superior to those of the parent alkaloids, i.e., ascididemin (I) and 2-bromoleptoclinidone (II).

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:369872 CAPLUS
DOCUMENT NUMBER: 136:151089
TITLE: Synthesis and electrophilic substitution of pyrido[2,3,4-kl]acridines
AUTHOR(S): Koller, Avi; Rudi, Amira; Garcia Gravalos, Marta; Kashman, Yoel
CORPORATE SOURCE: School of Chemistry, Tel Aviv University, Ramat Aviv, 69978, Israel
SOURCE: Molecules [online computer file] (2001), 6(4), 300-322
CODEN: MOLEFW; ISSN: 1420-3049
URL: http://www.mdpi.org/molecules/papers/60400300.pdf
PUBLISHER: Molecular Diversity Preservation International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Several new pyrido[2,3,4-kl]acridines were synthesized by reacting naphthoquinone, juglone, or cyclohexane-1,3-dione with .beta.,.beta.'-diamino ketones in a biomimetic reaction. The structures of all new compds. were elucidated by NMR and MS spectroscopy. Electrophilic substitution, mainly nitration, of the various compds. was undertaken and the substitution positions detd. A series of derivs. was prepd. and their cytotoxicity towards P-388 mouse lymphoma cells analyzed. The most cytotoxic derivs. were found to have IC50's of 0.05 and 0.1 .mu.g/mL.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137218 CAPLUS
DOCUMENT NUMBER: 134:193607
TITLE: Preparation of phenanthrolin-7-one derivatives and their therapeutic uses as **antitumoral** medicines
INVENTOR(S): Delfourne, Evelyne; Darro, Francis; Bastide, Jean; Kiss, Robert; Frydman, Armand
PATENT ASSIGNEE(S): Laboratoire L. Lafon, Fr.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012632	A2	20010222	WO 2000-FR2313	20000811
WO 2001012632	A3	20010719		

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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
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FR 2797446	A1	20010216	FR 1999-10493	19990813
FR 2797446	B1	20011102		
BR 2000013239	A	20020423	BR 2000-13239	20000811
EP 1202993	A2	20020508	EP 2000-958679	20000811

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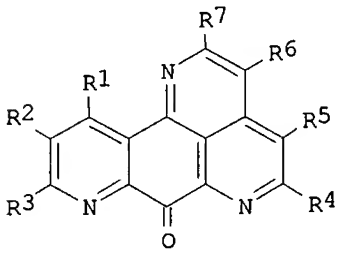
IE, SI, LT, LV, FI, RO, MK, CY, AL

NO 2002000669	A	20020415	NO 2002-669	20020211

PRIORITY APPLN. INFO.: FR 1999-10493 A 19990813
WO 2000-FR2313 W 20000811

OTHER SOURCE(S): CASREACT 134:193607; MARPAT 134:193607
GI



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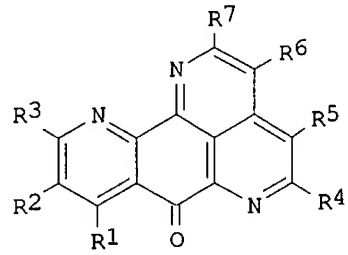

II

AB The invention concerns a pharmaceutical compn. comprising an efficient amt. of a compd. selected among the compds. I [R1, R2, R3, R4, R5 = H, halogen, C1-6-alkyl, OH, CHO, OR8, CO2H, CN, CO2R8, CONHR8, CONR8R9, NH2, NHR8, N(R8)2, NHCH2CH2NMe2, NHCH2CH2Cl, NHCOR8, morpholino, NO2, SO3H, CH2N(CO2R8)CH2CO2R9, CH2N(CO2R8)CH2Ar; R6 = H, halogen, C1-6-alkyl, (CH2)nR10, ; R7 = H, C1-6-alkyl, Ph-C1-4-alkyl, NR15R16; R8, R9 = C1-6-alkyl, Ph-C1-4-alkyl; R10 = halogen, OH, C1-6-alkoxy, OC(:O)-C1-6-alkyl, CN, CO2Et, COR11; R11 = Ph-C1-4-alkyl, NR12R13; R12 , R13 = H, C1-6-alkyl, Ph-C1-4-alkyl, (CH2)nR14; R14 = halogen, C1-6-alkoxy, NMe2; R15, R16 = H, C1-6-alkyl, Ph-C1-4-alkyl, (CH2)nR17; R17 = H, halogen, OH, C1-6-alkoxy; Ar = C6-14-aryl; n = 1 - 6] and II or their pharmaceutically acceptable salts. Thus, I [R1 = R2 = R3 = R4 = R5 = R6 = R7 = H (CRL8293)] and II [R1 = R2 = R3 = R4 = R5 = R6 = R7 = H (CRL8294)] were prepd. from quinoline-5,8-dione via Diels-Alder with crotonaldehyde dimethylhydrazone followed by cyclocondensation of the resulting quinone III with Me2NCMe(OEt)2. I (R1 = R2 = R3 = R4 = R5 = R6 = R7 = H) and II (R1 = R2 = R3 = R4 = R5 = R6 = R7 = H) have interesting cytotoxic properties [DMT = 10 mg/Kg (DMT = max. tolerable dose); -33% and -36%, resp. **tumor** surface diminution (murin mammary carcinoma (MXT-HI)}; -45% and -64% , resp. **tumor** surface diminution [(murin mammary adenocarcinoma (MXT-HS)}]; and, for II, T/C = 136% (lymphoma L1210)] leading to a therapeutic use as **antitumoral** medicines.

L6 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137217 CAPLUS
DOCUMENT NUMBER: 134:178717
TITLE: Ascididemin derivatives and their therapeutic

applications

INVENTOR(S): Delfourne, Evelyne; Darro, Francis; Bastide, Jean; Kiss, Robert; Frydman, Armand

PATENT ASSIGNEE(S): Laboratoire L. Lafon, Fr.

SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012631	A2	20010222	WO 2000-FR2312	20000811
WO 2001012631	A3	20010719		
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FR 2797445	A1	20010216	FR 1999-10490	19990813
FR 2797445	B1	20011102		
FR 2809399	A1	20011130	FR 2000-6652	20000524
BR 2000013249	A	20020416	BR 2000-13249	20000811
EP 1202992	A2	20020508	EP 2000-958678	20000811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507381	T2	20030225	JP 2001-517529	20000811
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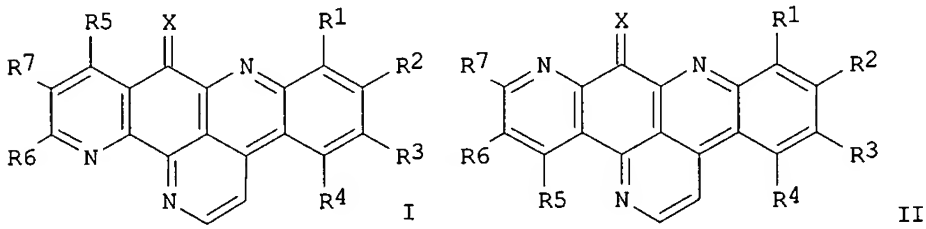
PRIORITY APPLN. INFO.:

FR 1999-10490	A	19990813
FR 2000-6652	A	20000524
WO 2000-FR2312	W	20000811

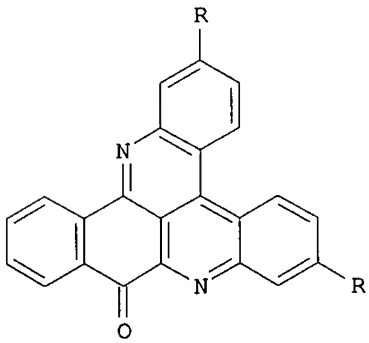
OTHER SOURCE(S): MARPAT 134:178717

GI



AB The invention discloses the prepn. and a pharmaceutical compn. comprising an efficient amt. of a compd. of formulas I and II [R1 = H, halogen, NO2, NR8R9 (R8, R9 = H, alkyl); R2 = H, halogen; R3 = H, halogen, alkyl, alkoxyl etc.; , R4 = H, halogen, NR8R9; R5-R7 = H, halogen, alkyl, carbonyloxyalkyl etc.; X = O, NH, NOH] for use as **antitumor** agent. Thus, ascididemin deriv. I [R1-R2,R4-R7 = H, R3 = Me; X = O] was prepd. via a multistep synthetic sequence starting from quinoline-5,8-dione, 5-methyl-2-amino acetophenone and DMF dimethylacetal. The prepd. ascididemin derivs. were tested for cytotoxic properties leading to a therapeutic use of these compds. as **antitumoral** medicines.

L6 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:133328 CAPLUS
DOCUMENT NUMBER: 134:353265
TITLE: Synthesis and electrophilic substitution of pyrido[2,3,4-kl]acridines
AUTHOR(S): Koller, Avi; Rudi, Amira; Gravalos, Marta Garcia; Kashman, Yoel
CORPORATE SOURCE: School of Chemistry, Tel Aviv University, Ramat Aviv, 69978, Israel
SOURCE: Proceedings of ECSOC-3, [and] Proceedings of ECSOC-4, Sept. 1-30, 1999 and 2000 (2000), Meeting Date 1999-2000, 675-682. Editor(s): Pombo-Villar, Esteban. Molecular Diversity Preservation International: Basel, Switz.
CODEN: 69AXZT
DOCUMENT TYPE: Conference; (computer optical disk)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:353265
GI



I

AB Several new pyrido[2,3,4-kl]acridines, e.g., I (R = H, OMe), were synthesized by reacting naphthoquinone, juglone and cyclohexane-1,3-dione with .beta.,.beta.'-diamino ketones in a biomimetic reaction. The structures of all new compds. were elucidated by NMR and mass spectroscopy. Electrophilic substitution, mainly nitration, of the various compds. was undertaken, and the substitution positions detd. A series of derivs. was prepd. and their cytotoxicity towards P-388 mouse lymphoma cells analyzed. The most cytotoxic derivs. were found to have IC50's of 0.1 .mu.g/mL.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:749926 CAPLUS
DOCUMENT NUMBER: 134:110200
TITLE: The mechanism of ascididemin-induced cytotoxicity
AUTHOR(S): Matsumoto, Sandra Sayuri
CORPORATE SOURCE: The Univ. Utah, USA
SOURCE: (2000) 128 pp. Avail.: UMI, Order No. DA9962074 From: Diss. Abstr. Int., B 2000, 61(2), 803
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L6 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:434886 CAPLUS
DOCUMENT NUMBER: 133:171833
TITLE: Inhibition of topoisomerase II by the marine alkaloid ascididemin and induction of apoptosis in leukemia cells
AUTHOR(S): Dassonneville, L.; Wattez, N.; Baldeyrou, B.; Mahieu, C.; Lansiaux, A.; Banaigs, B.; Bonnard, I.; Bailly, C.
CORPORATE SOURCE: IRCL, Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambret and INSERM U 524, Lille, 59045, Fr.
SOURCE: Biochemical Pharmacology (2000), 60(4), 527-537
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ascididemin (ASC) is a pentacyclic DNA-intercalating agent isolated from the Mediterranean ascidian Cystodytes dellechiajei. This marine alkaloid exhibits marked cytotoxic activities against a range of **tumor** cells, but its mechanism of action remains poorly understood. We investigated the effects of ASC on DNA cleavage by human topoisomerases I and II. Relaxation assays using supercoiled DNA showed that ASC stimulated double-stranded cleavage of DNA by topoisomerase II, but exerted only a very weak effect on topoisomerase I. ASC is a conventional topoisomerase II poison that significantly promoted DNA cleavage, essentially at sites having a C on the 3' side of the cleaved bond (-1 position), as obsd. with etoposide. The stimulation of DNA cleavage by topoisomerase I in the presence of ASC was considerably weaker than that obsd. with camptothecin. Cytotoxicity measurements showed that ASC was even less toxic to P388 leukemia cells than to P388CPT5 cells resistant to camptothecin. In addn., the marine alkaloid was found to be equally toxic to HL-60 leukemia cells sensitive or resistant to mitoxantrone. It is therefore unlikely that topoisomerases are the main cellular targets for ASC. This alkaloid was found to strongly induce apoptosis in HL-60 and P388 leukemia cells. Cell cycle anal. showed that ASC treatment was assocd. with a loss of cells in the G1 phase accompanied with a large increase in the sub-G1 region. Cleavage expts. with poly(ADP-ribose) polymerase (PARP) revealed that caspase-3 was a mediator of the apoptotic pathway induced by ASC. The DNA of ASC-treated cells was severely fragmented. Collectively, these findings indicate that ASC is a potent inducer of apoptosis in leukemia cells.

6 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:405130 CAPLUS
DOCUMENT NUMBER: 133:222875
TITLE: Preparation of new pyridoacridine derivatives and formal synthesis of 11-hydroxyascididemine
AUTHOR(S): Alvarez, Mercedes; Feliu, Lidia; Ajana, Wadi; Joule, John A.
CORPORATE SOURCE: Laboratori de Quimica Organica, Facultat de Farmacia, Universitat de Barcelona, Barcelona, E 08028, Spain
SOURCE: Tetrahedron (2000), 56(23), 3703-3708
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:222875
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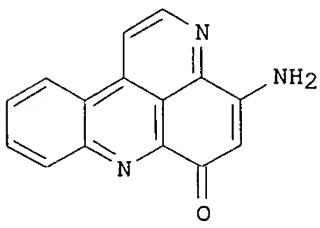

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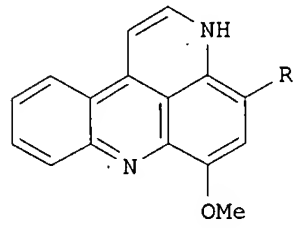
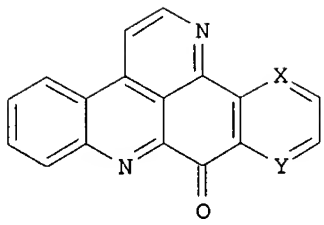


II

AB The prepn. of pyrido[2,3,4-kl]acridin-6-ones substituted at position 4 following our previous methodol. is described. A new synthetic route for the prepn. of aminopyridoacridone I used previously for the synthesis of the 11-hydroxyascididemine was described. The cytotoxic activity of pyridoacridones II (R = NO2, NHAc) in four cell lines was reported.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 10-17 l6 ibib abs

L6 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:176981 CAPLUS
DOCUMENT NUMBER: 132:293915
TITLE: Synthesis of ascididemine and an isomer
AUTHOR(S): Alvarez, Mercedes; Feliu, Lidia; Ajana, Wadi; Joule, John A.; Fernandez-Puentes, Jose Luis
CORPORATE SOURCE: Laboratori de Quimica Organica, Facultat de Farmacia, Universitat de Barcelona, Barcelona, 08028, Spain
SOURCE: European Journal of Organic Chemistry (2000), (5), 849-855
CODEN: EJOCFK; ISSN: 1434-193X
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:293915
GI



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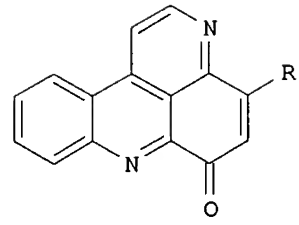


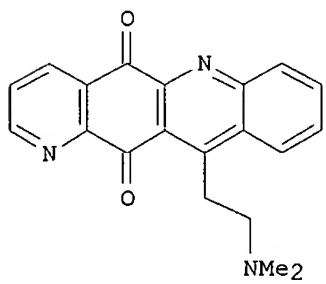
II

AB Ascididemine I (X = N, Y = CH) and its regioisomer I (X = CH, Y = N) were synthesized starting from 1,4-dimethoxy-9(10H)-acridinone. The acridone was converted into 1,4-dimethoxy-9-ethynylacridine by a triflate coupling. The ethynylacridine was converted in one-pot into 6-methoxy-(3H)-pyrido[2,3,4-kl]acridine by reaction with sodium diformylamide. The mechanism of this key cyclocondensation was discussed. Conversion into acridinones II (R = Br) and II (R = H), followed by reaction of each of these under high pressure conditions with acrolein N,N-dimethylhydrazone, gave regioselectively I and II, resp.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:97447 CAPLUS
DOCUMENT NUMBER: 132:265338
TITLE: Structural studies of cytotoxic marine alkaloids: synthesis of novel ring-E analogues of ascididemin and their in vitro and in vivo biological evaluation
AUTHOR(S): Lindsay, Brent S.; Christiansen, Holly C.; Copp, Brent R.
CORPORATE SOURCE: Department of Chemistry, University of Auckland, Auckland, N. Z.
SOURCE: Tetrahedron (2000), 56(3), 497-505
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:265338
GI



I

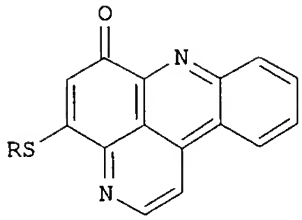
AB The cytotoxic marine alkaloid ascididemin and various pyridine ring-E analogs have been synthesized in an attempt to det. the pharmaceutical utility and structure-activity requirements for the parent alkaloid. All compds. synthesized were evaluated in a wide range of biol. screens for selective cytotoxicity, antiviral, antifungal and antimicrobial properties. Many analogs exhibited selective cytotoxicity to human solid **tumor** cell-lines in vitro, with I also exhibiting moderate

antitumor activity in in vivo xenograft assays.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:12269 CAPLUS
DOCUMENT NUMBER: 132:160772
TITLE: Interaction between **antitumor** drugs and a double-stranded oligonucleotide studied by electrospray ionization mass spectrometry
AUTHOR(S): Gabelica, Valerie; De Pauw, Edwin; Rosu, Frederic
CORPORATE SOURCE: Mass Spectrometry Laboratory, Chemistry Institute B6c, University of Liege, Liege, B-4000, Belg.
SOURCE: Journal of Mass Spectrometry (1999), 34(12), 1328-1337
CODEN: JMSPFJ; ISSN: 1076-5174
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Electrospray ionization mass spectrometry was used to investigate the complex formation between a double-stranded oligonucleotide and various **antitumor** drugs belonging to two categories: intercalators (ethidium bromide, amsacrine and ascididemin) and minor groove binders (Hoechst 33258, netropsin, distamycin A, berenil and DAPI). The goal of this study was to det. whether the relative intensities in the mass spectra reflect the relative abundances of the species in the soln. phase. The full-scan mass spectra suggest non-specific binding for the intercalators and specific binding for the minor groove binders. The preferential stoichiometries adopted by each minor groove binder were detd. by studying the influence of the drug concn. on the spectra. We obtained 2: 1>1: 1 for distamycin, 1: 1>2: 1 for Hoechst 33258 and DAPI and only the 1: 1 complex for netropsin and berenil. These features reflect their known behavior in soln. The compared tandem mass spectra of the 1:1 complexes with Hoechst 33258 and netropsin, when correlated with published crystallog. data, suggest the possibility of inferring some structural information. The relative binding affinities of the drug for the considered duplex were deduced with two by two competition expts., assuming that the relative intensities reflect the compn. of the soln. phase. The obtained affinity scale is netropsin > distamycin A > DAPI > Hoechst 33258 > berenil. These examples show some of the potential uses of mass spectrometry as a useful tool for the characterization of specific drug binding to DNA, and possibly a rapid drug screening method requiring small amts. of materials.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:404190 CAPLUS
DOCUMENT NUMBER: 131:243447
TITLE: A convenient new route to 4-substituted benzo[de][3,6]phenanthrolin-6(6H)-ones: important intermediates in the synthesis of ring-a analogues of the cytotoxic marine alkaloid ascididemin
AUTHOR(S): Copp, Brent R.; Hansen, Richard P.; Appleton, David R.; Lindsay, Brent S.; Squire, Chris J.; Clark, George R.; Rickard, Cliff E. F.
CORPORATE SOURCE: Department of Chemistry, University of Auckland, Auckland, N. Z.
SOURCE: Synthetic Communications (1999), 29(15), 2665-2676
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 131:243447
GI



I

AB 4-Ethylthio- and 4-(4-methylphenylthio)benzo[de][3,6]phenanthrolin-6(6H)-one I (R = EtS, 4-MeC6H4S) were synthesized in 4 steps from benzoquinone and then readily converted to the 4-amino and 4-methoxy analogs by nucleophilic substitution. Further elaboration leads to the synthesis of 11-hydroxyascididemin, which was found to exhibit antiviral activity in vitro.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:633418 CAPLUS
DOCUMENT NUMBER: 127:290836
TITLE: Plakinidine D, a new pyrroloacridine alkaloid from two ascidians of the genus Didemnum
AUTHOR(S): Smith, Cameron J.; Venables, Debra A.; Hopmann, Cordula; Salomon, Christine E.; Jompa, Jamaluddin; Tahir, Akbar; Faulkner, D. John; Ireland, Chris M.
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Natural Products (1997), 60(10), 1048-1050
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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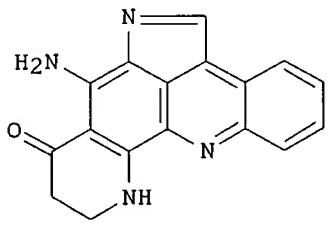
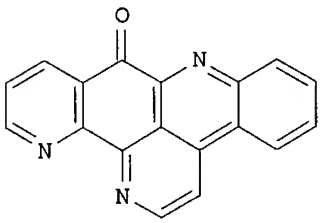


I

AB A previously undescribed red Didemnum sp. collected in Indonesia contained a novel pyrroloacridine, plakinidine D (I), along with the known compds. 3,5-diiodo-4-methoxyphenethylamine and ascididemin, both of which had previously been isolated from ascidians of the genus Didemnum. I and 3,5-diiodo-4-methoxyphenethylamine were also isolated from Didemnum rubeum from the Republic of Palau. Interestingly, a collection of D. rubeum from Indonesia did not contain I, but instead contained 3,5-diiodo-4-

methoxyphenethylamine and ascididemin. The structure of I was elucidated by anal. of its spectral data. I is closely related to plakinidines A-C, previously isolated from the sponge Plakortis sp.

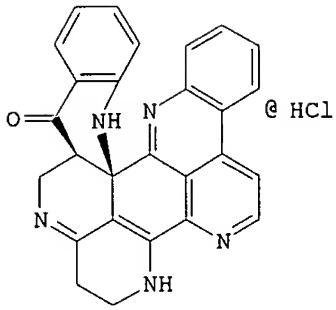
L6 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:519327 CAPLUS
DOCUMENT NUMBER: 122:305874
TITLE: Structural requirements for biological activity of the marine alkaloid ascididemin
AUTHOR(S): Lindsay, Brent S.; Barrows, Louis; Copp, Brent R.
CORPORATE SOURCE: Dep. Chem., Univ. Auckland, Auckland, 92019, N. Z.
SOURCE: Bioorganic & Medicinal Chemistry Letters (1995), 5(7), 739-42
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Comparison of the biol. activities obsd. for ascididemin (I) and synthetic precursors/analogs has established the importance of N-8 in ring A and a completed ring E to topoisomerase II enzyme inhibition, human **tumor** cytotoxicity, and antifungal/antibacterial properties. The results also suggest the presence of multiple mechanisms of toxicity by I towards mammalian cell systems.

L6 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:50478 CAPLUS
DOCUMENT NUMBER: 120:50478
TITLE: Two new polycyclic aromatic alkaloids from the Okinawan marine sponge Biemna sp
AUTHOR(S): Zeng, Chun Min; Ishibashi, Masami; Matsumoto, Keita; Nakaike, Shiro; Kobayashi, Junichi
CORPORATE SOURCE: Fac. Pharm. Sci., Hokkaido Univ., Sapporo, 060, Japan
SOURCE: Tetrahedron (1993), 49(37), 8337-42
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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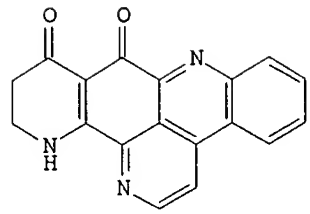

II

AB Two new polycyclic arom. alkaloids, biemnadin (I) and 8,9-dihydro-11-hydroxyascididemin (II), were isolated from the Okinawan marine sponge Biemna sp. The x-ray diffraction anal. of I established its octacyclic structure and the structure of II was elucidated on the basis of extensive spectroscopic and chem. studies. I and II exhibited cytotoxicity against human epidermoid carcinoma KB and murine lymphoma L1210 cells in vitro.

L6 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:84161 CAPLUS
DOCUMENT NUMBER: 112:84161
TITLE: An **antitumor** pentacyclic alkaloid from Didemnum
INVENTOR(S): Kobayashi, Junichi; Oizumi, Yasushi
PATENT ASSIGNEE(S): Mitsubishi Kasei Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 2 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01186885	A2	19890726	JP 1988-7480	19880119

PRIORITY APPLN. INFO.: JP 1988-7480 19880119
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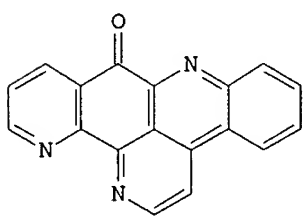

I

AB The title compd., ascididemin (I), useful as an **antitumor** agent, is isolated from Didemnum species. A homogenate (500 g) of a Didemnum species was extd. with 1500 mL MeOH twice, the ext. concd. to dryness, 150 mL H2O added, and the resulting mixt. extd. with 150 mL EtOAc 3 times to give, after concn. and chromatog. over silica gel with MeOH-CHCl3 (5:95), a yellow solid I. In an in vitro study using mouse leukemia cells L 1210, I showed an IC50 of 0.39 .mu.g/mL.